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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/734,759	12/11/2003	Thomas John Goodwin	MSC-22859-3-CU	2623

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NASA JOHNSON SPACE CENTER
MAIL CODE HA
2101 NASA RD 1
HOUSTON, TX 77058

EXAMINER	
FORD, ALLISON M	

ART UNIT	PAPER NUMBER
1651	

DATE MAILED: 01/25/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/734,759	GOODWIN ET AL.	
	Examiner	Art Unit	
	Allison M. Ford	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 November 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *36-42 and 44-51* is/are pending in the application.

4a) Of the above claim(s) *36-41,44 and 45* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *42 and 46-51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group II, claim 42, in the reply filed on 9 November 2005 is acknowledged. New claims 45-51, directed to the method of claim 42, have been added. Claims 36-42 and 44-51 are pending in the current application, with claims 36-41 and 44 being withdrawn from consideration. Claims 42 and 46-51 have been examined on the merits.

Priority

Acknowledgement is made of the current applications claim for priority as a continuation of application 09/532001 (now US Patent 6946246), which is a divisional of application 09/056363 (now US Patent 6730498), which further claims priority to provisional application 60/043205. However, in order to claim the benefit of a prior-filed application a specific reference to the prior-filed application(s) in compliance with 37 CFR 1.78(a) must be included in the first sentence(s) of the specification following the title or in an application data sheet. For benefit claims under 35 U.S.C. 120, 121 or 365(c), the reference must include the relationship (i.e., continuation, divisional, or continuation-in-part) of the applications. It is noted applicant has made specific reference to the provisional application 60/043205, but no reference is made to the parent non-provisional applications.

The later-filed application (current application) must be an application for a patent for an invention which is also disclosed in the prior application(s) (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35

U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed applications, Application Nos. 09/532001, 09/056363, and 60/043205, all fail to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. The currently examined claims are directed to the culture of renal stem cells in a rotating wall vessel; none of the parent applications teach culture of renal stem cells in any capacitation, rather they are limited in scope to mature kidney cells. Culture of stem cells requires unique considerations and conditions compared to mature cells, they are recognized as distinct and unique in the field of cell and tissue culture. Therefore, because none of the parent applications specifically teach the culture of renal stem cells, or any stem cells, the currently claimed invention (claims 42 and 45-51) is not granted priority to any of the parent applications. The effective filing date of claims 42 and 45-51 is determined to be the filing date of the present application, 11 December 2003.

Claim Objections

Claim 1 is objected to because of the term "culture matrix;" though the term is not so unclear so as to render the claim indefinite, the examiner feels the more art accepted terminology would be 'matrix material,' or 'cell culture matrix;' change to a more art-accepted term is suggested.

Claim 51 is objected to because of a spelling error, "Coriolis forces" is incorrectly spelled "coriolus forces." Correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 42 and 46-51 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant's claims are directed to a method of producing active renal epithelial cells comprising: isolating renal stem cells; and culturing said renal stem cells in a rotating wall vessel containing a cell culture comprising culture media and culture matrix, wherein gravity is substantially balanced in said rotating wall vessel by equal and opposite physical forces. Applicant's invention requires directed differentiation of renal stem cells to renal epithelial cells; however, the specification does not mention any method involving renal stem cells, or their directed differentiation to renal epithelial cells. What is not mentioned is certainly not described. Thus, the specification provides no information or guidance for directing the differentiation of renal stem cells to produce active renal epithelial cells. Consequently, applicants were not in possession of the claimed invention at the time of filing, and claims 42 and 46-51 fail to satisfy the written description requirement.

Claims 42 and 46-51 are further rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicant's claims are directed to a method of producing active renal epithelial cells comprising: isolating renal stem cells; and culturing said renal stem cells in a rotating wall vessel containing a cell

culture comprising culture media and culture matrix, wherein gravity is substantially balanced in said rotating wall vessel by equal and opposite physical forces.

Applicant's invention requires directed differentiation of renal stem cells to renal epithelial cells; directed differentiation of stem cells would be extremely useful for in vitro production of artificial tissue constructs and for in vivo or ex vivo organ regeneration; however, while much research is being conducted, understanding of the differentiation pathways and successful methods of directed differentiation are limited. Furthermore, applicants are claiming a method of culturing and differentiating "renal stem cells," such a term is interpreted in its broadest sense to include any stem cell which has the potential to differentiate into renal cells, this genus therefore includes embryonic stem cells (which have pluripotent potential to develop into all cell types), as well as neural stem cells and bone marrow stromal cells (See Poulsom et al, Pg. 448, col. 1 & Table 1). But applicants have not provided any information on any type of renal stem cell, and no teachings on methods of directing such differentiation. As a result, the scope of the instant claims, directed differentiation of any 'renal stem cell' to renal epithelial cells, is not commensurate with the enablement of the instant disclosure, which is limited to culture of mature kidney cells, because practice of the claimed invention would require undue experimentation by an artisan of ordinary skill to elicit the specific methods required to direct differentiation of any and all types of 'renal stem cells' to renal epithelial cell morphology. The instant specification is not enabling for claims drawn to directed differentiation of renal stem cells to renal epithelial cells.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the

invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Directed differentiation of stem cells is a highly controversial subject with little consensus within the skilled community; while some groups have reported successful results, others are often unable to replicate the methods. Regarding use of embryonic stem cells, the specific signals which triggers differentiation down specific cell lineage pathways are still not well understood (See Vats et al, Pg. 600). With regards to 'renal stem cells' there is still no evidence that a true 'renal stem cell' exists (See Anglani et al, Pg. 475, col. 1); therefore there are no teachings on how to direct differentiation of such a cell. Much focus has been placed on transdifferentiation of cells of non-renal origin for development of kidney cells; for example, Poulom et al describe the transdifferentiation of bone marrow stromal cells to renal cells, but they also admit other studies found contradictory results (See Poulom et al, Pg. 448, col. 2). In general, the nature of stem cell differentiation is very complex; the breadth of the current invention (use of any renal stem cell) encompasses an extremely broad scope that is not supported by the present specification, nor is there evidence in the art enabling for the entire scope.

The present specification provides zero examples involving renal stem cells; nor does the specification even provide teachings or direction regarding the specific culture conditions which are needed to correctly differentiate renal stem cells to renal epithelial cells. Therefore, based on the unpredictability of the art and the complete absence of teachings or working examples provided in the present specification, the current specification is not enabled for the directed differentiation of any type of

renal stem cell to renal epithelial cells, and one of ordinary skill in the art would not have a reasonable expectation of successfully producing active renal epithelial cells by performing the claimed method.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 42 and 46-51 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicant's claims are directed to a method of producing active renal epithelial cells comprising: isolating renal stem cells; and culturing said renal stem cells in a rotating wall vessel containing a cell culture comprising culture media and culture matrix, wherein gravity is substantially balanced in said rotating wall vessel by equal and opposite physical forces.

In claim 42 it is not clear what is meant by "active renal epithelial cells," is not clear if applicant is intending to require the renal epithelial cells *actively* produce or secrete a desired compound, or if the renal epithelial cells must just be *active,* such as undergoing division, differentiation and growth.

Furthermore, in claim 42 the step of culturing the renal stem cells in a rotating wall vessel containing a cell culture renders the claim indefinite, as it is not clear if the rotating wall vessel must contain a separate cell culture, therefore the renal stem cells are co-cultured with another cell population, or if applicant intends for the renal cell culture to be the cell culture referred to. It appears the latter interpretation is correct, such that the renal stem cells are cultured in a rotating wall vessel containing culture media and a 'culture matrix.'

The term "substantially" in claim 42 is a relative term which renders the claim indefinite. The term "substantially" is not defined by the claim, the specification does not provide a standard for

ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Therefore the claim is rendered indefinite because one skilled in the art cannot determine the metes and bounds of the claimed subject matter.

Finally, in claim 42 the preamble does not appear to be commensurate in scope with the body of the claim. The preamble describes a method of producing active renal epithelial cells; one of ordinary skill in the art would interpret renal epithelial cells to refer to mature, differentiated renal epithelial cells which line the tubules of the kidneys. However, the body of the claim describes isolation and culture of renal stem cells, without providing steps or direction for directed differentiation of the renal *stem* cells to mature renal epithelial cells. Therefore it is unclear how the renal epithelial cells recited in the preamble are produced; it appears the method is omitting essential steps relating to the differentiation of the renal stem cells.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 42 and 46-51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Humes et al (US Patent 6,410,320), in view of Goodwin et al (J Cell Biochem, 1993), Uemura et al (US 2003/0064513 A1), Unsworth et al (Nature Medicine, 1998), and Hammond et al (Am J Physiol Renal Physiol, 2001).

Applicant's claim 42 is directed to a method of producing active renal epithelial cells comprising: isolating renal stem cells; and culturing said renal stem cells in a rotating wall vessel containing a cell culture comprising culture media and culture matrix, wherein gravity is substantially balanced in said

rotating wall vessel by equal and opposite physical forces. Claim 45 requires the culture matrix to be microcarrier beads. Claim 46 requires the active renal epithelial cells to be suitable for therapeutic uses. Claim 47 requires the active renal epithelial cells to be suitable for diagnostic uses. Claim 48 requires the active renal epithelial cells to be human. Claim 49 requires the physical forces to comprise sedimentational shear stress. Claim 49 requires the physical forces to comprise sedimentational shear stress and centrifugal forces. Claim 51 requires the physical forces to comprise viscosity and Coriolis forces.

Humes et al teach a method of producing renal epithelial cells from renal tubule stem cells, comprising isolating renal tubule stem cells from adult mammalian (rabbit) kidneys, culturing the cells in standard culture dishes to a confluent monolayer, and then treating the tissue culture with TGF-β1, EGF, and retinoic acid (See Col. 7, ln 55-col. 8 ln 22). After 144 hours of treatment with the TGF-β1, EGF, and retinoic acid Humes et al report formation of cell aggregates comprising a well defined lumen bordered by epithelial tubule cells.

Though Humes et al do not culture the renal tubule stem cells in a rotating wall vessel, at the time the invention was made it would have been well within the purview of one of ordinary skill in the art to alternatively culture the renal tubule stem cells in a rotating wall vessel under appropriate conditions to create the cell aggregates containing epithelialized tubules.

At the time the invention was made it was well known that cell assembly in three-dimensional culture conditions results in a more natural cell assembly, and helps to promote more elaborate, sophisticated cell-to-cell architecture and differentiation that better imitates those created *in vivo,* than compared to culture in two-dimensional conditions (See, e.g. Unsworth et al, Pg. 901). Among the three-dimensional culture methods simulated microgravity, created by rotating wall vessels (RWV), was recognized as superior due to the reduction of the detrimental forces of high sheer stress that were problematic in many of the other three-dimensional cultures (i.e. roller culture, spinner flasks, etc).

Unsworth et al teach that a variety of cells cultured in simulated microgravity in RWVs form differentiated, tissue-like 3-D constructs (See Unsworth et al, Pg. 903). For example, Goodwin et al had successfully cultured baby hamster kidney cells (BHK-21 cells) in a rotating wall vessel system to create three-dimensional, functional (as in the cell aggregates continued to grow and secrete enzymes), kidney cell aggregates (See Goodwin et al, Pg 305, col. 2- Pg 306, col. 1). Goodwin et al managed to culture the adherent kidney cells in the suspension culture by utilizing microcarrier beads, to which the kidney cells could adhere and grow (See Goodwin et al, pg. 304, col. 1). Additionally, Uemura et al teach that undifferentiated cells (i.e. stem and/or progenitor cells) can be successfully cultured and differentiated in rotating wall vessels (See Uemura et al, Pg. 2-3 paragraphs 0047-0049).

Based on the teachings of Unsworth et al one of ordinary skill in the art would have been motivated to perform the culture method of Humes et al in a rotating wall vessel in order to produce differentiated kidney cell aggregates with a more natural cell assembly that better imitates the cell-to-cell architecture found *in vivo*. Furthermore, based on the teachings of Goodwin et al, one of ordinary skill in the art would have been motivated to utilize microcarrier beads to provide a substrate for attachment of the renal tubule stem cells within the cell culture suspension (Claim 45).

One of ordinary skill in the art would have a reasonable expectation that the culture conditions described by Humes et al could be replicated in a rotating wall vessel system to successfully differentiate the renal stem cells into kidney cell aggregates comprising lumens lined with epithelial cells because the RWV culture system was known to be a suitable modification/improvement over two-dimensional culture methods for culture of three-dimensional cell aggregates (See Unsworth et al), kidney cells, specifically, were known to successfully form aggregates in RWV culture systems (See Goodwin et al), and because it was known that RWV culture systems were suitable for culture and differentiation of undifferentiated cells (See Uemura et al). Therefore, based on the teachings in the prior art one would have a reasonable

expectation of successfully performing the culture method of Humes et al, to produce renal epithelial cells, in a RWV (Claim 42).

Furthermore, though Humes et al experiment with rabbit kidney cells, at the time the invention was made, it would have been well within the purview of one of ordinary skill in the art to alternatively culture human renal cells (Claim 48). One of ordinary skill in the art would have been motivated to perform the method of Humes et al, modified to involve culturing in a RVW, as above, using human renal cells in order to produce human renal cell aggregates comprising renal epithelial cells. Human kidney aggregates would be useful for testing and diagnostic purposes, as well as providing cells that could potentially function as tissue transplants, in place of organ donations (See Unsworth et al). One would have a reasonable expectation that the method of Humes et al could be successfully performed on human renal cells because Humes et al showed success with rabbit renal cells, another form of mammalian cells; because mammalian cells have similar physiology between species one would have a reasonable expectation of applying the culture method to other mammals, including humans.

Applicants have not specifically pointed out any special or unique features of the active renal epithelial cells created by the claimed method that would not be inherently shared by any renal epithelial cell; therefore, the renal epithelial cells created by Humes et al, which could be produced by culturing in a rotating wall vessel, as above, would be considered suitable for therapeutic and/or diagnostic use (Claims 46 and 47).

Finally, the rotating wall vessel described by Unsworth et al and Goodwin et al appears to be the same rotating wall vessel, developed by NASA, as used in the current application; even if the actual devices were in fact not identical, they at least operate on the same principle of simulated microgravity created by rotation around a horizontal axis with zero head space within the culture. Therefore, because the RWV relied upon for the current rejection operates on the same principles as that of the current invention, the RWV of the prior art also balances gravity by equal and opposite physical forces, wherein

the physical forces comprise sedimentational shear stress, centrifugal forces, viscosity and Coriolis forces (See Hammond et al) (Claims 49-51).

Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Allison M. Ford whose telephone number is 571-272-2936. The examiner can normally be reached on 7:30-5 M-Th, alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Allison M Ford
Examiner
Art Unit 1651